Oncogenic action of PBF in head and neck cancer is associated with poorer overall survival

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Introduction

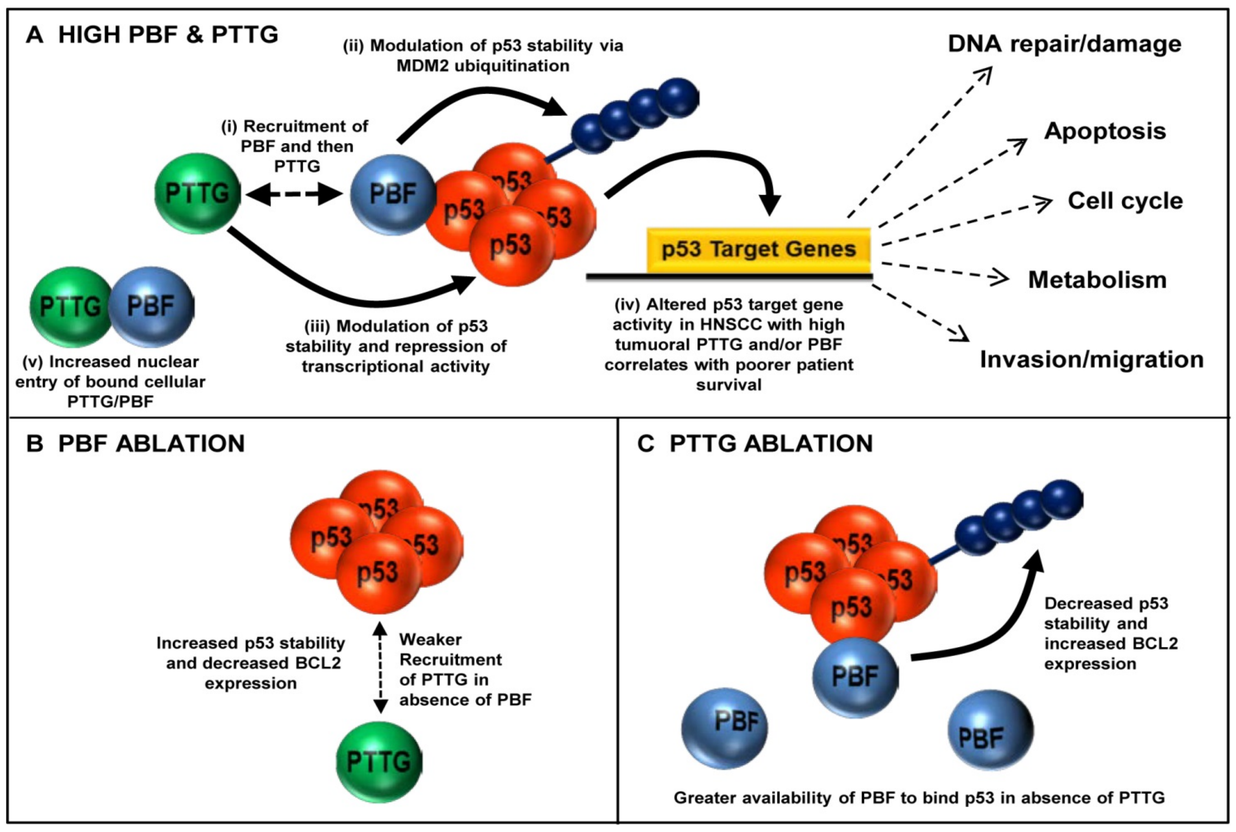
PBF is a multifunctional proto-oncogene overexpressed in thyroid and other endocrine cancers. Previously we identified a functional interaction between PBF and the tumour suppressor p53 in well-differentiated thyroid cancer (WDTC). Here, we delineate the oncogenic mechanisms of PBF, along with its binding partner PTTG, in head and neck cancer (HNSCC), in which loss of function of p53 is common by TP53 mutation, interaction with the HPV E6 oncoprotein or by loss of heterozygosity (LOH).

Aims

To determine the role of PBF and PTTG in HNSCC by studying:

- **Tumour expression levels**
- **Impact on p53 stability and target genes**
- **Patient survival**

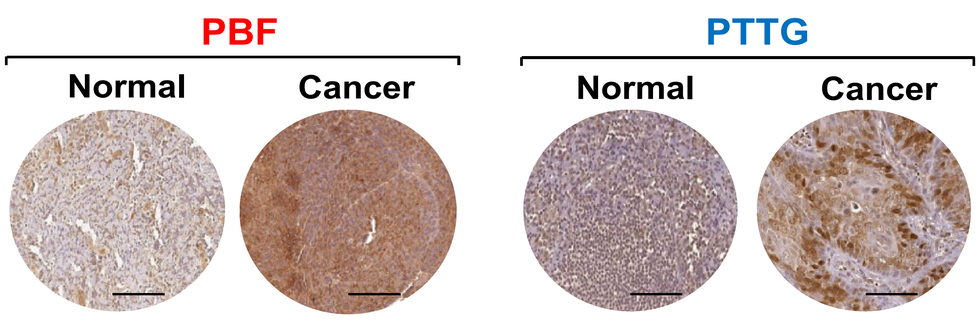
Proposed model of PBF, PTTG and p53 interaction



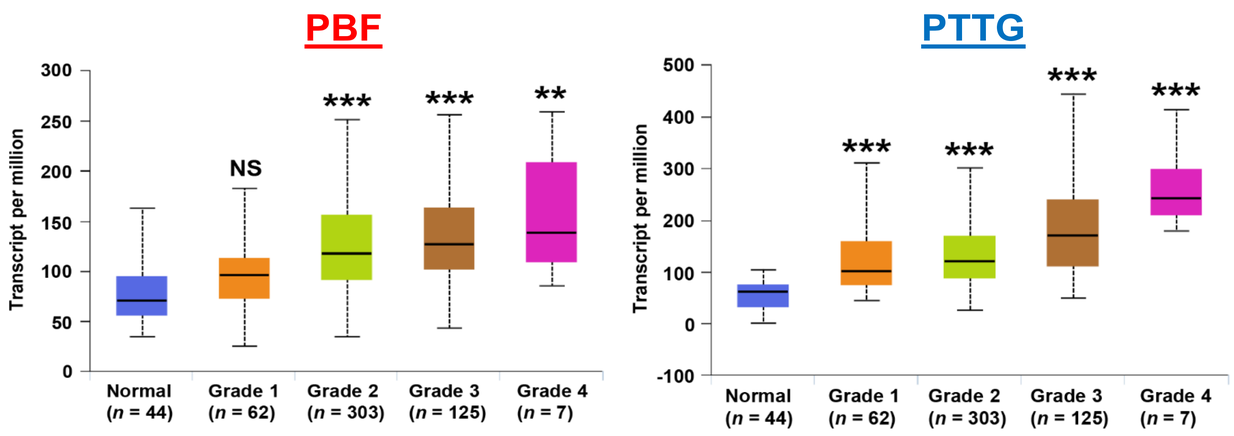
Elevated expression of PBF and PTTG in HNSCC

PBF and PTTG were abundantly overexpressed in HNSCC in (i) Tumour tissue (*n* = 53) and (ii) TCGA data (*n* = 497)

(i)

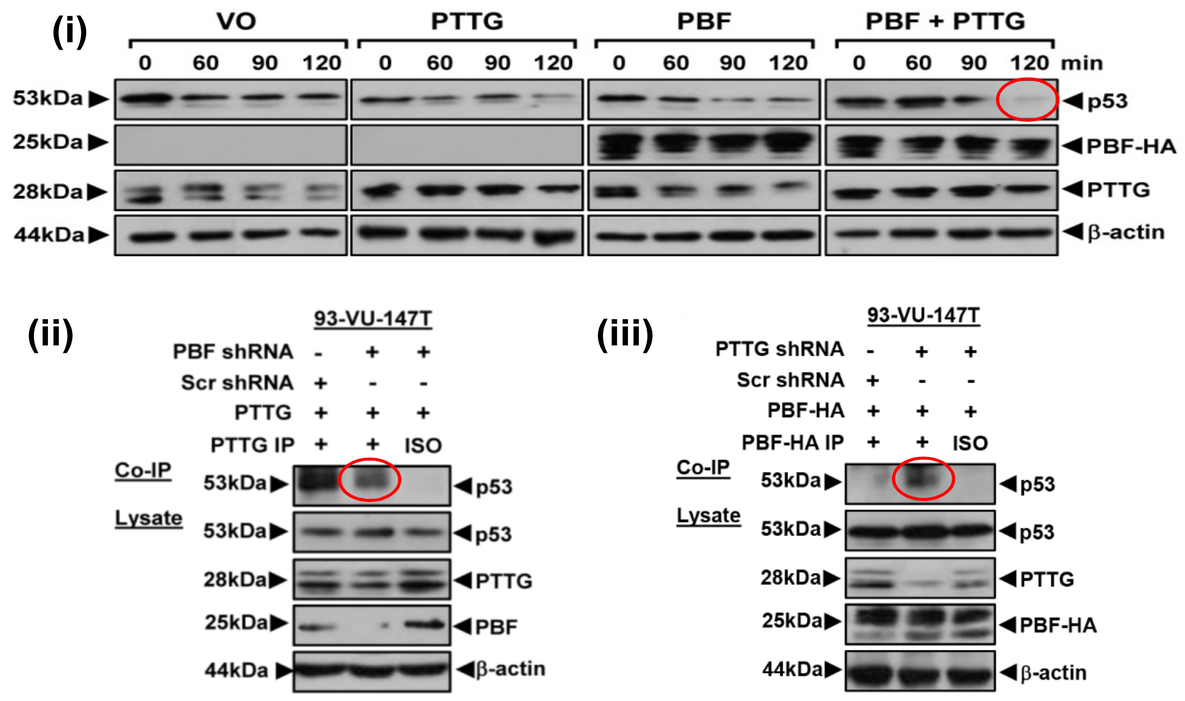


(ii) Expression of PBF and PTTG in HNSCC based on tumour grade



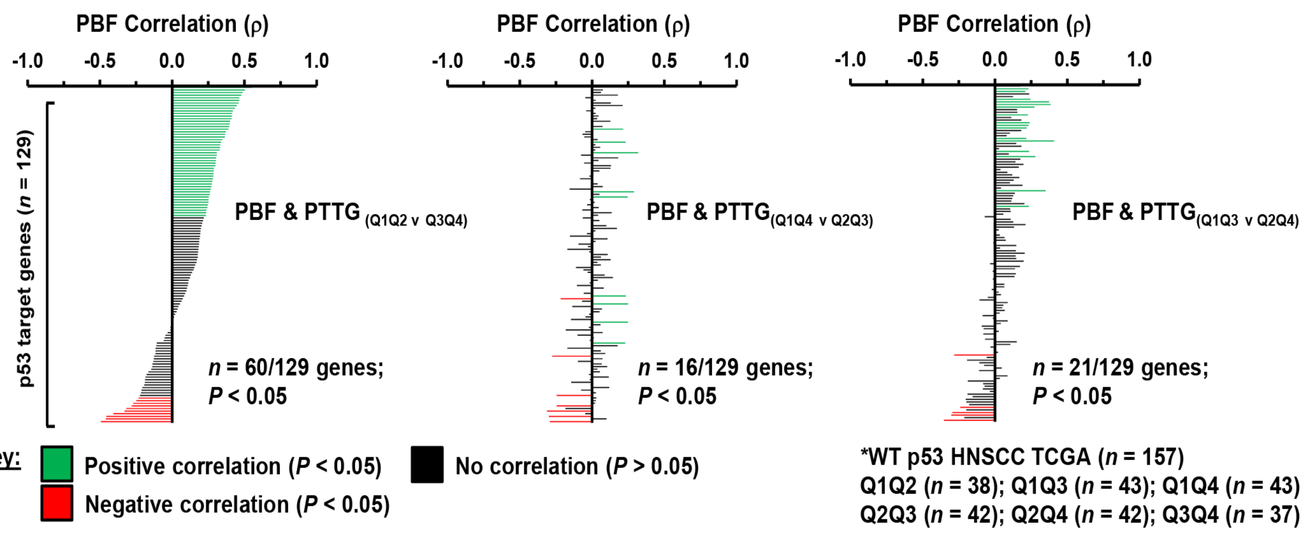
PBF and PTTG alter p53 protein stability

(i) PBF and PTTG alone caused a significant increase in p53 protein turnover (~6-fold). Co-expression of both PBF and PTTG resulted in the greatest reduction in p53 protein stability (13-fold).



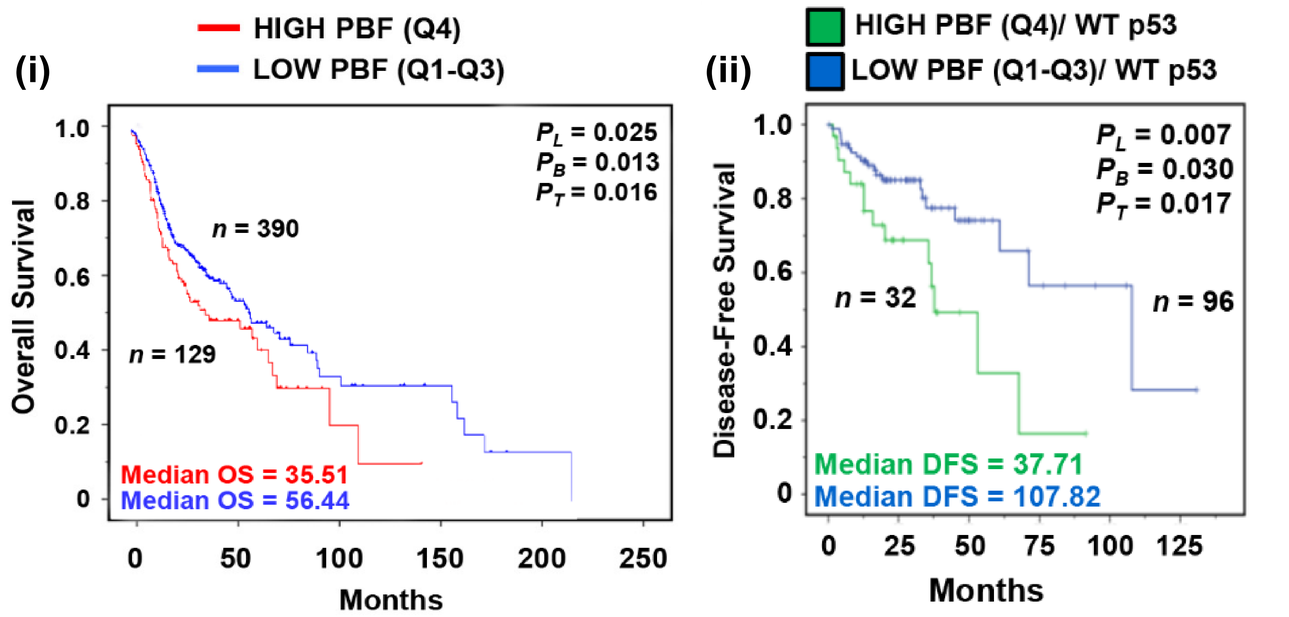
(ii) PTTG retained the ability to bind p53 in the absence of PBF, but the degree of interaction was attenuated. (iii) Whereas PBF binding to p53 was markedly increased in the absence of PTTG.

Correlation of PBF with p53-target genes



An important transcriptional relationship between PBF and p53 was highlighted by extensive correlation between PBF expression with 129 p53-target genes in wild-type p53 HNSCC (high PBF/PTTG versus low PBF/PTTG expression; left - 60/129 genes). In contrast, fewer p53 target genes were correlated with PBF in different PBF/PTTG expression subgroups (middle - 16/129 genes; right - 21/129 genes).

High PBF expression is associated with poorer survival



Summary

This is the first study to show that PBF is of critical relevance to head and neck cancer. HNSCC patients with high tumoural PBF and PTTG have worse outcomes due in part to greater aberration of p53-dependent signalling.

References

[1]Read ML *et al.* PTTG and PBF Functionally Interact with p53 and Predict Overall Survival in Head and Neck Cancer. *Cancer Research* 2018 Oct 15;78(20):5863-5876

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Neoplasia, cancer and late effects

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